Genetic Polymorphisms in Base-Excision Repair Pathway Genes and Risk of Breast Cancer

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Abstract

Impaired base-excision repair (BER) function can give rise to the accumulation of DNA damage and initiation of cancer. We evaluated whether genetic variation in six BER pathway genes (*XRCC1, ADPRT, APEX1, OGG1, LIG3*, and *MUTYH*) is associated with breast cancer risk in two large population-based case-control studies in the United States (3,368 cases and 2,880 controls) and Poland (1,995 cases and 2,296 controls). A detailed evaluation was first done in a subset of 1,898 cases and 1,514 controls with mouthwash DNA samples in the U.S. study. Significant findings were followed up in the remainder of the U.S. study population that provided cytobrush DNA samples and in the Polish study. Using data from U.S. study participants with mouthwash DNA, we found no significant overall association between breast cancer risk and *XRCC1 R280H* and *R194W, ADPRT V726W, APEX1 D148E, OGG1 S326C, LIG3 R780H*, or *MUTYH* 5′ untranslated region. These data suggested a decreased risk for *XRCC1Q399R* homozygous variants compared with homozygous wild-type in premenopausal women, but these findings were not confirmed when data from cytobrush DNA samples were added [combined odds ratio (OR), 0.8; 95% confidence interval (95% CI), 0.6-1.1] or in the Polish study (OR, 1.0; 95% CI, 0.7-1.5). Meta-analyses based on our data and published data from studies of two single nucleotide polymorphisms in *XRCC1* showed no evidence of an overall association between breast cancer risk and homozygous variants versus wild-type for *Q399R* (OR, 1.1; 95% CI, 1.0-1.2) or *R194W* (OR, 1.0; 95% CI, 0.7-1.8), although there was a suggestion for an association in Asian populations for *Q399R* (OR, 1.6; 95% CI, 1.1-2.4; $P = 0.02$). In conclusion, our results do not support that the polymorphisms evaluated in six BER pathway genes play a major role in breast carcinogenesis, particularly in Caucasian populations. (Cancer Epidemiol Biomarkers Prev 2006;15(2):353–8)

Introduction

Genetic variation in DNA repair genes could cause altered DNA repair function, resulting in accumulation of DNA damage, followed by programmed cell death (apoptosis) or unregulated cell growth and cancer. Base-excision repair (BER) is an important DNA repair pathway responsible for the repair of base damage resulting from X-rays, oxygen radicals, and alkylating agents (1-3). Two major processes are included in BER: releasing the damaged base by DNA glycosylases and core BER reaction, including cleavage of the sugar-phosphate chain, excision of the abasic residue, and local DNA synthesis and ligation (2). Epidemiologic studies have linked single nucleotide polymorphisms (SNP) in both DNA glycosylase and BER core protein genes to human cancer risk including breast cancer (3, 4).

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BER includes many proteins and the genes encoding them have numerous genetic variants. XRCC1 acts as a central scaffolding protein by binding DNA ligase III, DNA polymerase β, and poly(ADP-ribose) polymerase in BER (5-8). Two common genetic polymorphisms in *XRCC1* (*Q399R* and *R194W*) have been evaluated in relation to breast cancer risk in several previous studies (9-20). The results, however, have been inconsistent. It has also been suggested that the relationship between *XRCC1 Q399R* and *R194W* and breast cancer risk might be modified by ethnicity or by family history (9-19). Polymorphisms of other genes in the BER pathway and breast cancer risk have been less explored. For this project, we analyzed eight SNPs in six BER genes (*XRCC1, ADPRT, APEX1, OGG1, LIG3*, and *MUTYH*) in one of the largest population-based case-control studies of breast cancer conducted to date, which includes 3,368 cases and 2,880 controls in the United States. We also evaluated polymorphisms in *XRCC1 Q399R* in a case-control study of 1,995 cases and 2,296 controls in Poland.

Materials and Methods

Study Population

The U.S. Breast Cancer Study. Eligible cases were English-speaking female residents of Wisconsin, western Massachusetts, or New Hampshire; of ages 20 to 74 years; and with a recent primary diagnosis of invasive or *in situ* breast cancer reported to the states' mandatory cancer registries between

1998 and 2001. Controls were randomly selected from population lists (licensed motor vehicle drivers for women of ages 20-64 years and Medicare beneficiaries for women of ages 65-74 years) in each state and frequency matched by 5 year categories to the age distribution of the cases. Women provided a telephone interview, covering known and suspected risk factors for breast cancer, and were invited to participate in buccal cell collection at the end of the interview. Initially, buccal cells were collected using two buccal cytobrushes (June 1998-December 1999) with the collection method later changed to a mouthwash protocol to improve DNA quality (January 2000-March 2001). Samples were returned to a National Cancer Institute (NCI)–affiliated laboratory for processing. Collection, storage, and DNA isolation protocols have been previously described (21). The study was reviewed and approved by local institutional review boards (IRB) and the NCI IRB. All participants provided written informed consent.

Approximately 80% of eligible breast cancer cases and 75% of eligible controls completed the interview. Respective participation rates for buccal cell collection in cases and controls who completed the interview were 73% and 64% for cytobrush samples and 71% and 61% for mouthwash samples. Because of insufficient DNA quantity or quality, 596 of 2,097 cases and 588 of 1,993 controls with a cytobrush sample and 22 of 1,986 cases and 14 of 1,573 controls with a mouthwash sample were excluded from genotype analyses. To limit heterogeneity, analyses were further restricted to Caucasian women, mostly of central European ancestry, resulting in a total of 1,470 cases (1,311 invasive and 159 *in situ*) and 1,366 controls with cytobrush DNA and 1,898 cases (1,661 invasive and 237 *in situ*) and 1,514 controls with mouthwash DNA samples included in the analyses.

The Polish Breast Cancer Study. Eligible cases were women 20 to 74 years of age, residents of Warsaw and Lodz in Poland, and newly diagnosed with either histologically or cytologically confirmed *in situ* or invasive breast cancer between January 2000 and January 2003. Cases were recruited through a rapid identification system organized at participating hospitals. The Cancer Registry in Warsaw was used to identify the eligible cases missed by the rapid case identification system in each hospital. The Polish Electronic System, a database with demographic information from all residents of Poland, was used to randomly select controls stratified by city and age in 5 year categories on a quarterly basis from January 2000 to September 2003. Women provided a personal interview on known and suspected risk factors. Venous blood samples were collected by a trained nurse and DNA was isolated from buffy coat or whole blood samples. The study protocol was reviewed and approved by local and NCI IRBs. All participants provided written informed consent. Of the 3,037 eligible cases and 3,639 controls, 2,386 (79%) cases and 2,502 (69%) controls agreed to participate in the personal interview. The present study is limited to women with DNA isolated from blood samples: 1,995 (84%) cases and 2,296 (94%) controls.

Genotyping. We selected eight SNPs in six BER genes with assays available at the time of analysis at the Core Genotyping Facility of the Division of Cancer Epidemiology and Genetics, NCI. We chose SNPs that have been previously examined in relation to breast cancer [*XRCC1 Q399R* (rs25487; refs. 9-20), *R280H* (rs25489; ref. 13), *R194W* (rs1799782; refs. 9-12, 14, 17-20), and *OGG1 S326C* (rs1052133; ref. 22)] or had possible functional significance, such as missense variants [*ADPRT V726W* (rs1136410), *APEX1 D148E* (rs3136820), *LIG3 R780H* (rs3136025)] or variants in regulatory sequences [*MUTYH* 5′ untranslated region (5′ UTR), rs3219466]. DNA was extracted from mouthwash samples collected in the U.S. breast cancer study and was genotyped for the eight SNPs at the Core Genotyping Facility of NCI. DNA extracted from cytobrush samples collected in the U.S. study and blood DNA samples from the Polish study were genotyped for *XRCC1 Q399R* (rs25487). Description and methods for each genotype assay can be found at http://snp500cancer.nci.nih.gov (23). Duplicated DNA samples were included for quality control (150 cytobrush DNA and 187 mouthwash DNA in the U.S. study and 100 blood DNA in the Polish study). All assays had ≥99% concordance rates, except for *XRCC1 R280H* (98%), in the U.S. study. We observed no significant departures from Hardy-Weinberg equilibrium in the U.S. Caucasian or Polish control populations for any of the SNPs analyzed (Table 1). Three different types of DNA sources (mouthwash, cytobrush, and blood) were used for genotyping *XRCC1 Q399R*. The minor allele frequencies among controls were very similar for different DNA sources (35.3% in mouthwash, 37.8% in cytobrush, and 36.2% in blood).

Data Analysis. Associations between genotypes and breast cancer risk were initially evaluated using mouthwash DNA samples from the U.S. study participants. Polymorphisms associated with breast cancer risk ($P < 0.05$) in these analyses were then evaluated using cytobrush DNA samples from the U.S. participants and blood DNA samples from the Polish study participants. Unconditional logistic regression was used to estimate odds ratios (OR) and their 95% confidence intervals (95% CI) for the associations between genetic polymorphisms of the BER pathway and breast cancer risk. Potential confounding variables included in the final models were only age and study site. Additional adjustment for body mass index, family history of breast cancer in first-degree relatives, age at menarche, age at first full term pregnancy, parity, age at menopause, menopausal status, hormone replacement therapy, and highest level of education did not result in a material change in the observed associations. Analyses were done using SAS statistical software, version 8.02 (SAS Institute, Inc., Cary, NC).

Meta-analyses. Meta-analyses were done to summarize our findings along with those of published studies of the association between breast cancer risk and two polymorphisms in *XRCC1 (Q399R* and *R194W)*. Peer-reviewed studies published in June 2005 in English on the relationship between *XRCC1* and breast cancer risk were located using *PubMed*. Crude ORs and 95% CIs were calculated for all studies using published frequencies for cases and controls by the genotype of interest. Analyses were conducted overall and separately in Caucasian and Asian women. A random-effect model (24) in STATA (Version 8.2, Special Edition) was employed to estimate summary ORs and 95% CIs by weighing each study result by a factor of within- and between-study variance. Homogeneity of study results in different groups was assessed by the Q test and publication bias by Begg's test (25) and Egger's test (26).

Results

As shown in Table 1, analysis of data from mouthwash DNA samples in the U.S. study (1,898 cases and 1,514 controls) showed no significant association between *XRCC1 R280H, ADPRT V762A, APEX1 D148E, OGG1 S326C, LIG3 R780H*, and *MUTYH* 5′ UTR and breast cancer risk overall or by menopausal status. However, in premenopausal women, those who carried the homozygous A genotype of *XRCC1 Q399R* had a significantly reduced risk of breast cancer compared with women who carried the homozygous G genotype (OR, 0.6; 95% CI, 0.4-0.9). The interaction between menopausal status and *XRCC1 Q399R* was not statistically significant ($P_{\text{interaction}} = 0.20$). Further assessment of this finding, using the cytobrush DNA available from the U.S. study (1,470 cases and 1,366 controls), showed no significant reduction in risk overall or for either premenopausal or postmenopausal women. We also found little evidence of an association when the mouthwash and cytobrush data were combined. Further evaluation of the

Table 1. Associations between genetic polymorphisms in BER pathway and risk of breast cancer among Caucasians in the U.S. breast cancer study

SNP (dbSNP ID)	Genotype	Overall		Premenopausal		Postmenopausal	
		Cases/Controls	OR* (95% CI)	Cases/Controls	OR* (95% CI)	Cases/Controls	OR* (95% CI)
XRCC1 (Q399R)†	GG	659/505	1.0	252/159	1.0	366/307	1.0
(rs25487)	AG	769/590	1.0 (0.9-1.2)	310/234	0.8 (0.7-1.1)	408/322	1.1 (0.9-1.3)
P_{HWE} = 0.36	AA	207/192	0.8 (0.7-1.1)	72/75	0.6 (0.4-0.9)	122/97	1.1 (0.8-1.5)
	P_{trend}		0.19		0.01		0.58
XRCC1 (Q399R)‡	GG	555/549	1.0	223/177	1.0	289/344	1.0
(rs25487)	AG	664/583	1.2 (1.0-1.4)	254/184	1.1 (0.9-1.5)	352/358	1.2 (1.0-1.5)
P_{HWE} = 0.50	AA	185/168	1.1 (0.9-1.4)	77/51	1.2 (0.8-1.9)	97/109	1.0 (0.8-1.4)
	P_{trend}		0.20		0.24		0.43
XRCC1 (Q399R)§	GG	1,214/1,054	1.0	475/336	1.0	655/651	1.0
(rs25487)	AG	1,433/1,173	1.1 (0.9-1.2)	564/418	1.0 (0.8-1.2)	760/680	1.1 (0.9-1.3)
P_{HWE} = 0.25	AA	392/360	0.9 (0.8-1.1)	149/126	0.8 (0.6-1.1)	219/206	1.1 (0.8-1.3)
	P_{trend}		0.92		0.27		0.36
XRCC1 (R280H)†	GG	1,403/1,122	1.0	536/391	1.0	776/642	1.0
(rs25489)	AG	157/113	1.1 (0.8-1.4)	61/46	1.0 (0.6-1.4)	84/62	1.1 (0.8-1.6)
P_{HWE} = 0.93	AA	4/3	1.0 (0.2-4.3)	1/2	0.3 (0.0-3.5)	3/1	2.2 (0.2-21.2)
	P_{trend}		0.51		0.65		0.43
XRCC1 (R194W)†	CC	1,384/1,086	1.0	526/397	1.0	769/606	1.0
(rs1799782)	CT	189/156	0.9 (0.8-1.2)	80/50	1.2 (0.8-1.8)	94/94	0.8 (0.6-1.0)
P_{HWE} = 0.05	TT	7/11	0.5 (0.2-1.4)	1/1	0.6 (0.0-10.3)	6/10	0.5 (0.2-1.4)
	P_{trend}		0.29		0.33		0.03
ADPRT (V762A)†	CC	1,194/963	1.0	472/351	1.0	646/543	1.0
(rs1136410)	CT	468/361	1.0 (0.9-1.2)	170/129	1.0 (0.7-1.3)	264/208	1.1 (0.9-1.3)
P_{HWE} = 0.07	TT	54/47	0.9 (0.6-1.4)	24/14	1.3 (0.7-2.5)	28/25	0.9 (0.5-1.6)
	P_{trend}		0.97		0.76		0.90
APEX1 (D148E)†	TT	404/327	1.0	161/116	1.0	218/187	1.0
(rs3136820)	GT	752/590	1.0 (0.9-1.2)	284/210	1.0 (0.7-1.3)	414/330	1.1 (0.8-1.4)
P_{HWE} = 0.46	GG	373/290	1.0 (0.8-1.3)	142/108	1.0 (0.7-1.4)	207/162	1.1 (0.8-1.4)
	P_{trend}		0.74		0.78		0.59
OGG1 (S326C)†	CC	967/760	1.0	373/278	1.0	516/422	1.0
(rs1052133)	CG	532/424	1.0 (0.8-1.2)	202/143	1.1 (0.8-1.4)	306/250	1.0 (0.8-1.2)
P_{HWE} = 0.93	GG	72/60	1.0 (0.7-1.4)	28/25	0.9 (0.5-1.5)	41/29	1.2 (0.7-1.9)
	P_{trend}		0.78		0.88		0.60
LIG3 (R780H)†	GG	1,559/1,237	1.0	595/440	—	860/701	1.0
(rs3136025)	AG	9/3	2.6 (0.7-9.7)	2/0	—	7/3	2.0 (0.5-7.7)
P_{HWE} = 0.97	AA	0/0	—	0/0	—	0/0	—
	P_{trend}		0.17				0.39
MUTYH†	CC	1,493/1,164	1.0	579/416	1.0	813/657	1.0
(rs3219466)	CT	98/96	0.8 (0.6-1.1)	33/35	0.7 (0.4-1.1)	61/56	0.9 (0.6-1.3)
P_{HWE} = 0.50	TT	2/1	2.0 (0.2-21.6)	0/0	—	2/1	1.9 (0.2-20.9)
	P_{trend}		0.16		0.13		0.47

NOTE: P_{HWE}, P value for departures of Hardy-Weinberg equilibrium among control populations.
*Adjusted for age and study site.
† Including subjects in mouthwash study.
‡ Including subjects in cytobrush study.
§Including subjects in both mouthwash and cytobrush studies.

association using the data from Poland also showed no significant association overall or by menopausal status (Table 2).

In postmenopausal women, those who carried the heterozygous or homozygous T genotype of *XRCC1 R194W*, compared with those who carried the homozygous C genotype, had a nonsignificantly reduced risk of breast cancer [OR, 0.8 (95% CI, 0.6-1.0) and OR, 0.5 (95% CI, 0.2-1.4), respectively; Table 1] although the test of linear trend was significant (P = 0.03).

Further analyses in the U.S. breast cancer study stratified by family history of breast cancer in first-degree relatives did not modify the associations between SNPs in *XRCC1, ADPRT, APEX1, OGG1, LIG3*, and *MUTYH* genes and breast cancer risk (data not shown). Findings were also similar for *in situ* and invasive breast cancer (data not shown). Pairwise D' values, estimated using HaploView (27), indicated that the three *XRCC1* SNPs are in strong linkage disequilibrium in the U.S. breast cancer study ($D' > 0.96$) although the correlation between SNPs was low ($r^2 < 0.05$).

Meta-analyses. Results from meta-analyses of two polymorphisms (*Q399R* and *R194W*) in the *XRCC1* gene are presented in Table 3. The meta-analyses summarize the data presented here from the U.S. and Polish studies, data from 12 studies (9-20) that investigated the relationship between *Q399R* and breast cancer risk and 9 studies (9-12, 14, 17-20) that investigated the relationship with *XRCC1 R194W*. Summary estimates showed no significant associations between these two SNPs and breast cancer risk in all women (total of 10,934 cases and 11,543 controls for *Q399R* and total of 5,752 cases and 6,050 controls for *R194W*) or in separate analyses of Caucasian women (total of 7,824 cases and 8,226 controls for *Q399R* and total of 3,822 cases and 4,015 controls for *R194W*). However, in Asian women (total of 1,567 cases and 1,643 controls), we noted a significant 60% increased risk for women who carried homozygous A genotype compared with women who carried homozygous G genotype of *XRCC1 Q399R* (95% CI, 1.1-2.3). We found no significant study heterogeneity according to the Q test or publication bias according to Begg's or Egger's tests for either overall populations or different ethnic groups (data not shown).

Discussion

Using data from two large population-based case-control studies of Caucasian women in the United States and Poland,

Table 2. Association between XRCC1 *Q399R* genotype and breast cancer risk in the Polish breast cancer study

SNP (dbSNP ID)	Genotype	Overall		Premenopausal		Postmenopausal	
		Cases/Controls	OR* (95% CI)	Cases/Controls	OR* (95% CI)	Cases/Controls	OR* (95% CI)
XRCC1 (*Q399R*)	GG	772/947	1.0	191/273	1.0	546/633	1.0
(rs25487)	AG	933/1,030	1.1 (1.0-1.3)	236/289	1.2 (0.9-1.5)	650/693	1.1 (0.9-1.3)
$P_{HWE} = 0.15$	AA	280/313	1.1 (0.9-1.4)	63/90	1.0 (0.7-1.5)	194/213	1.1 (0.8-1.3)
	P_{trend}		0.13		0.53		0.39

NOTE: P_{HWE}, P value for departures of Hardy-Weinberg equilibrium among control populations.
*Adjusted for age and study site.

we found no evidence to support that the common genetic variants in six BER genes (*XRCC1, ADPRT, APEX1, OGG1, LIG3*, and *MUTYH*) evaluated in this report play a major role in breast carcinogenesis. Evidence from a meta-analysis based on both prior published studies and the two studies in this report further supported a lack of association between two common genetic variants in *XRCC1* (*Q399R* and *R194W)* and breast cancer risk in Caucasian populations. However, the meta-analysis suggested an increased risk for *XRCC1 Q399R* homozygous variants compared with homozygous wild-type in Asian populations.

Epidemiologic studies of *XRCC1 Q399R* and breast cancer risk have provided some evidence of increased risk associated with the A allele among African Americans (9) and Asians (10, 18). Studies among Caucasians, however, have consistently found no association (11-17, 19). The lack of association in Caucasian populations was confirmed by both the U.S. and Polish breast cancer studies in this report. Summary estimates from our meta-analysis (total of 7,824 cases and 8,226 controls) showed no evidence of an association between *XRCC1 Q399R* and breast cancer risk in Caucasian populations [OR, 1.0 (95% CI, 0.9-1.1), for homozygous variants versus wild-type]. However, when the meta-analysis was restricted to four studies of Asian populations (total of 1,567 cases and 1,643 controls), there was a significant 60% increased risk for *XRCC1 Q399R* homozygous variants versus wild-type (OR, 1.6; 95% CI, 1.1-2.4). Only one study including 253 cases and 266 controls evaluated the association between *XRCC1 Q399R* and breast cancer risk among African Americans, noting an 70% increased risk associated with heterozygous or homozygous A genotype (OR, 1.7; 95% CI, 1.1-2.4; ref. 9). The frequency of the variant A allele was significantly different among the three

Table 3. Meta-analysis of the effects of *XRCC1 Q399R* and *R194W* on breast cancer risk

Study		Country	Ethnicity	Cases	Controls	OR (95% CI)	*P*	OR (95% CI)	*P*	References
XRCC1 Q399R						AG vs GG		cAA vs GG		
Chacko	2005	India	Asian	123	123	2.0 (1.2-3.5)	0.01	2.7 (1.1-6.4)	0.03	18
Deligezer	2004	Turkish	Asian	151	133	0.9 (0.5-1.5)	0.65	1.3 (0.6-2.6)	0.52	17
Smith	2003	United States	Caucasian	162	302	0.8 (0.5-1.2)	0.33	1.1 (0.6-2.1)	0.78	12
Kim	2002	Korea	Asian	205	205	0.8 (0.5-1.2)	0.20	2.4 (1.2-4.7)	0.01	10
Forsti	2004	Finland	All	223	298	1.1 (0.8-1.6)	0.60	0.9 (0.5-1.7)	0.71	20
Smith	2003	United States	Caucasian	253	268	1.2 (0.8-1.7)	0.45	1.2 (0.7-2.1)	0.53	11
Duell	2001	United States	Black	253	266	1.5 (1.1-2.3)	0.03	2.1 (0.6-7.3)	0.24	9
Moullan	2003	France	Caucasian	254	312	0.9 (0.6-1.3)	0.57	1.0 (0.6-1.6)	0.87	13
Duell	2001	United States	Caucasian	386	381	1.1 (0.8-1.5)	0.46	0.8 (0.5-1.3)	0.44	9
Figueiredo	2004	Canada	Caucasian	402	402	0.9 (0.7-1.2)	0.59	0.9 (0.6-1.4)	0.7	16
Han	2003	United States	Caucasian	1,004	1,385	1.0 (0.9-1.2)	0.66	1.1 (0.8-1.4)	0.61	14
Shen	2005	United States	All	1,067	1,110	1.1 (0.9-1.3)	0.38	1.0 (0.7-1.3)	0.79	19
Shu	2003	China	Asian	1,088	1,182	1.0 (0.8-1.1)	0.69	1.2 (0.9-1.7)	0.19	15
This study		Poland	Caucasian	1,995	2,296	1.1 (1.0-1.3)	0.11	1.1 (0.9-1.3)	0.33	
This study		United States	Caucasian	3,368	2,880	1.1 (0.9-1.2)	0.31	0.9 (0.8-1.1)	0.5	
Meta-analysis										
All studies (N = 14)				10,934	11,543	1.1 (1.0-1.1)	0.13	1.1 (1.0-1.2)	0.24	
Studies of Caucasian populations (N = 8)				7,824	8,226	1.1 (1.0-1.1)	0.13	1.0 (0.9-1.1)	0.81	
Studies of Asian populations (N = 4)				1,567	1,643	1.0 (0.8-1.4)	0.85	1.6 (1.1-2.3)	0.02	
XRCC1 R194W						CT/TT vs CC*				
Chacko	2005	India	Asian	123	123	2.0 (1.1-3.5)	0.02			18
Deligezer	2004	Turkish	Asian	151	133	0.5 (0.2-1.2)	0.11			17
Duell	2001	United States	Black	161	166	0.7 (0.4-1.2)	0.23			9
Smith	2003	United States	Caucasian	162	302	1.1 (0.6-2.0)	0.69			12
Kim	2002	Korea	Asian	205	205	1.1 (0.7-1.6)	0.69			10
Forsti	2004	Finland	All	223	298	1.3 (0.6-2.6)	0.52			20
Duell	2001	United States	Caucasian	251	234	0.7 (0.3-1.4)	0.32			9
Smith	2003	United States	Caucasian	253	268	1.7 (1.0-2.9)	0.07			11
Moullan	2003	France	Caucasian	254	312	1.0 (0.6-1.7)	0.91			13
Han	2003	United States	Caucasian	1,004	1,385	0.8 (0.6-1.0)	0.1			14
Shen	2005	United States	All	1,067	1,110	0.9 (0.7-1.2)	0.61			19
This study		United States	Caucasian	1,898	1,514	0.9 (0.7-1.1)	0.46			
Meta-analysis										
All studies (N = 11)				5,752	6,050	1.0 (0.8-1.2)	0.87			
Studies of Caucasian populations (N = 6)				3,822	4,015	0.9 (0.8-1.1)	0.54			
Studies of Asian populations (N = 3)				479	461	1.1 (0.6-2.1)	0.79			

*CT and TT genotypes were combined because some studies did not show data for the two genotypes separately.

ethnic groups (Caucasian, 36%; Asian, 30%; African, 14%; P = 0.0006), which was very similar with the number from a recently published meta-analysis of *XRCC1* polymorphisms and cancer risk (28). Summary estimates for *XRCC1 Q399R* homozygous variants versus wild-type and overall cancer risk presented in that meta-analysis (28) are consistent with an increased risk in Asian (OR, 1.16; 95% CI, 0.98-1.38) or African (OR, 1.43; 95% CI, 0.68-2.99) populations, but not in European populations (OR, 0.96; 95% CI, 0378-1.19). However, it is unclear that the observed differences by race have a biological basis and genetic effects for complex diseases tend to be consistent across human populations (29). Therefore, further evidence is needed to make a conclusion about potential differences in relative risk by race.

Studies of *XRCC1 R194W* and breast cancer risk have been inconsistent, with some suggesting an increased risk (11, 18), a reduced risk (9, 14, 17), or no association (10, 13, 19). We found no association in the U.S. women, and summary estimates from our meta-analysis provided no evidence of an association either among all populations [OR, 1.0 (95% CI, 0.8-1.2), based on 5,752 cases and 6,050 controls] or Caucasians [OR, 0.9 (95% CI, 0.8-1.1), based on 3,822 cases and 4,015 controls]; this result was also supported by a previous meta-analysis (28).

Very few studies have investigated associations between other genetic variants in BER pathway and breast cancer risk. One study in Asians (123 cases and 123 controls) found no association between *XRCC1 R280H* and breast cancer risk (18). One study among Caucasians (254 cases and 312 controls) reported an 80% increased risk associated with the *XRCC1 R280H* homozygous or heterozygous A genotype (13). However, this increased risk was not confirmed in the present study of U.S. women. We also found no association between *OGG1 S326C* and breast cancer risk, consistent with a previous study of 434 cases and 434 controls (22).

A strength of our investigation is the availability of two large population-based studies in Caucasian populations with good participation rates. The mouthwash component of the U.S. study that was used to screen for potentially interesting findings had sufficient power to detect small to moderate associations between the genetic polymorphisms evaluated and risk of breast cancer. Additional samples from women with cytobrush DNA in the U.S. study allowed a substantial increase in sample size to assess potential associations, and the Polish study served as an independent replication study. The analytic strategy also minimized the probability of reporting false-positive findings. Finally, compared with a recently published meta-analysis (28), our meta-analyses had substantially larger number of breast cancer cases (2,382 in Hu et al.'s study versus 10,934 in ours for *Q399R* and 2,476 versus 5,752 for *R194W*) and controls (2,780 versus 11,543 for *Q399R* and 2,122 versus 6,050 for *R194W*). The meta-analyses for associations evaluated in previous studies permitted a more definite conclusion about these associations. Although this is a large study, the power to detect associations with rare SNPs (i.e., *XRCC1 R280H, XRCC1 R194W, LIG3 R780H*, and *MUTYH 5′ UTR*) was limited, resulting in relatively wide confidence intervals. We used an approach that preferentially selected coding SNPs in candidate genes and did not perform a dense survey of SNPs intended to characterize haplotype diversity. Therefore, it is possible that common genetic variation in the BER genes not captured by our approach could be related to breast cancer risk. Other alternative approaches, such as selecting haplotype tagging SNPs, should be considered.

In summary, we provide evidence against a substantial association between *XRCC1 Q399R* and *R194W* and breast cancer risk, with the possible exception of an association for *Q399R* in Asian populations. The U.S. breast cancer study also showed no evidence for an association with SNPs evaluated in other BER genes and the results were not changed after stratified by menopausal status and family history. These findings indicate that the genetic variants in six BER genes evaluated in this report are unlikely to play a major role on breast carcinogenesis, particularly in Caucasian populations.

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